CLAIMS

1. A transgenic knockout mouse whose genome comprises a homozygous disruption in its endogenous FcRn gene, wherein said homozygous disruption prevents the expression of a functional FcRn protein, resulting in a transgenic knockout mouse in which exogenously administered IgG1 exhibits a substantially shorter half-life, as compared to the half-life of exogenously administered IgG1 in a wild-type mouse.

2. A transgenic knockout mouse whose genome comprises a homozygous disruption in its endogenous FcRn gene, wherein said homozygous disruption prevents the expression of a functional FcRn protein, resulting in a transgenic knockout mouse which is unable to absorb maternal IgG in the prenatal or neonatal stage of development.

3. The transgenic knockout mouse of Claim 1 or 2 wherein the homozygous disruption results from deletion or mutation of portions of the endogenous FcRn gene whereby a non-functional gene product or complete absence of the gene product is produced.

4. The transgenic knockout mouse of Claim 3 wherein the deleted portion of the endogenous FcRn gene is replaced with a neomycin-resistance cassette.

5. The transgenic knockout mouse of Claim 3 wherein the homozygous disruption consists of a deletion of 853 nucleotides of sequences upstream of exon 1, the entirety of exon 1 and intron 1, and 207 nucleotides immediately downstream of intron 2 of the FcRn gene,

and wherein the deleted portion of the endogenous FcRn gene is replaced with a neomycin-resistance cassette.

6. A method of producing a monoclonal antibody which specifically binds FcRn through its antigen binding regions, comprising:
   a) providing a FcRn-/- transgenic knockout mouse described in Claim 1;
   b) immunizing the FcRn-/- transgenic knockout mouse with FcRn;
   c) generating a hybridoma which secretes a monoclonal antibody which specifically binds FcRn through its antigen binding regions from B-cells isolated from the immunized mouse; and
   d) isolating the monoclonal antibody which specifically binds FcRn through its antigen binding regions from the hybridoma.

7. The monoclonal antibody produced by the method of Claim 6.

8. The monoclonal antibody of Claim 7 which binds to human FcRn.

9. The monoclonal antibody of Claim 7 which, when bound to FcRn, inhibits binding of FcRn to the Fc region of IgG.

10. A monoclonal antibody which specifically binds FcRn through its antigen binding regions and, when bound to FcRn, inhibits binding of FcRn to the Fc region of IgG.

11. The monoclonal antibody of Claim 7 which binds to the FcRn/β2M complex but does not bind to β2M alone or β2M complexed with any other molecule other than FcRn and inhibits binding of the FcRn/β2M complex to the Fc region of IgG.

12. The monoclonal antibody of Claim 7 which inhibits the formation of the FcRn/β2M complex by inhibiting binding of FcRn to β2M.

13. A method to detect FcRn molecules using the monoclonal antibody of Claim 7, said method consisting, but not limited to, enzyme-linked immunoassays (ELISA), radio-immunosorbent assay (RIA), immunoperoxidase-based in situ staining assay, antibody-based lateral flow assay and flow-cytometry assay.

14. A mouse model for autoimmune disease in humans for use in developing human FcRn based therapeutics, the mouse being a transgenic knockout mouse whose genome comprises a homozygous disruption in its endogenous FcRn gene, wherein said homozygous disruption prevents the expression of a functional FcRn protein, the mouse also being transgenic for expression of functional huFcRn protein from a complete huFcRn gene.

15. The mouse model of claim 14 wherein the transgenic knockout mouse is further characterized as having an NZM2410/J, BXSB/MpJ, BXSB/MpJ-Yaa, MRL-MPJ, or MRL-MPJ-Faslpr background or any other mouse genotype backgrounds that are used in autoimmune studies.

16. The mouse model of claim 14 wherein the transgenic knockout mouse is further characterized as having other known genes expressed in the muFcRn-/-, +huFcRn transgenic mouse that are important in autoimmune disease pathways.

17. The mouse model of Claim 14 wherein the huFcRn gene further comprises about 10 kb 5' and about 10 kb 3' sequences which flank the huFcRn gene in the human genome, and includes all known normal regulatory sequences.

18. A mouse model for autoimmune disease in humans for use in developing human FcRn based therapeutics, the mouse being a transgenic knockout mouse whose genome comprises a homozygous disruption in its endogenous FcRn gene, wherein said homozygous disruption prevents the expression of a functional FcRn protein, the mouse also being transgenic for expression of functional huFcRn protein from a huFcRn cDNA construct.

19. The mouse model of claim 18 wherein the transgenic knockout mouse is further characterized as having an NZM2410/J, BXSB/MpJ, BXSB/MpJ-Yaa, MRL-MPJ, or MRL-MPJ-Faslpr background or any other mouse genotype backgrounds that are used in autoimmune studies.

20. The mouse model of claim 18 wherein the transgenic knockout mouse is further characterized as having other known genes expressed in the muFcRn-/-, +huFcRn transgenic mouse that are important in autoimmune disease pathways.

21. The mouse model of Claim 18 wherein the huFcRn gene further comprises an FcRn cDNA construct containing regulatory sequences that produce variable to abnormally higher levels of protein expression than found with transgenes driven by endogenous FcRn regulatory sequences.

22. A mouse model for autoimmune disease in humans for use in developing human FcRn based therapeutics, the mouse being a transgenic knockout mouse whose genome comprises a homozygous disruption in its endogenous FcRn and IgG gene, wherein said homozygous disruption prevents the expression of a functional FcRn and IgG protein, the mouse also being transgenic for expression of functional huFcRn protein from a huFcRn DNA construct and human IgG from a huIgG DNA construct, wherein the huFcRn protein in the mouse functions to protect human IgG from degradation.

23. A mouse model for autoimmune disease in humans for use in developing human FcRn based therapeutics, the mouse being a transgenic knockout mouse whose genome comprises a homozygous disruption in its endogenous FcRn gene, wherein said homozygous disruption prevents the expression of a functional FcRn protein, the mouse also being transgenic for expression of functional huFcRn protein from a huFcRn DNA construct and human IgG from a huIgG DNA construct, wherein the huFcRn protein in the mouse functions to protect human IgG from degradation.

24. A method to identify or characterize an inhibitor of FcRn mediated protection of IgG antibodies, comprising:

a) providing functional huFcRn/huβ2M complexes in solution or bound to a support;

b) contacting candidate inhibitor to the huFcRn/huβ2M complex;

c) contacting human IgG to the huFcRn/huβ2M complex under conditions appropriate for binding of the huFcRn/huβ2M complex to the human IgG; and

d) assaying for inhibition of binding due to the candidate inhibitor, as compared to binding of a control huFcRn/huβ2M complex to human IgG in the absence of candidate inhibitor.

25. A method to identify or characterize an inhibitor of FcRn mediated protection of IgG antibodies, comprising:

a) providing functional huFcRn/huβ2M complexes in solution or bound to a support;

b) contacting human IgG to the huFcRn/huβ2M complex under conditions appropriate for binding of the huFcRn/huβ2M complex to the human IgG;

c) contacting candidate inhibitor to the huFcRn/huβ2M; and

d) assaying for inhibition of binding due to the candidate inhibitor, as compared to binding of a control huFcRn/huβ2M complex to human IgG in the absence of candidate inhibitor.

26. A method to identify or characterize an inhibitor of FcRn comprising:

a) providing mammalian cells in culture which functionally express huFcRn;

b) contacting candidate inhibitor to the mammalian cells of step a);

c) contacting human IgG to the mammalian cells; and

d) assaying IgG catabolism by the mammalian cells in the presence and absence of candidate inhibitor, with an increase in IgG catabolism in the presence

of candidate inhibitor, as compared to IgG catabolism in the absence of candidate inhibitor, being an indication that the candidate inhibitor inhibits huFcRn.

27. A method to identify or characterize an inhibitor of FcRn comprising:
    a) providing mouse FcRn-/-,+huFcRn cells in culture;
    b) contacting candidate inhibitor to the FcRn-/-,+huFcRn cells of step a);
    c) contacting human IgG to the FcRn-/-,+huFcRn cells; and
    d) assaying IgG catabolism by the mammalian cells in the presence and absence of candidate inhibitor, with an increase in IgG catabolism in the presence of candidate inhibitor, as compared to IgG catabolism in the absence of candidate inhibitor, being an indication that the candidate inhibitor inhibits huFcRn.

28. A method to identify or characterize an inhibitor of FcRn comprising:
    a) providing mammalian cells in culture which functionally express huFcRn;
    b) contacting human IgG to the mammalian cells of step a);
    c) contacting candidate inhibitor to the mammalian cells; and
    d) assaying IgG catabolism by the mammalian cells in the presence and absence of candidate inhibitor, with an increase in IgG catabolism in the presence of candidate inhibitor, as compared to IgG catabolism in the absence of candidate inhibitor, being an indication that the candidate inhibitor inhibits huFcRn.

29. A method to identify or characterize an inhibitor of FcRn comprising:
    a) providing mouse FcRn-/-,+huFcRn cells in culture;
    b) contacting human IgG to the FcRn-/-,+huFcRn cells of step a);
    c) contacting candidate inhibitor to the FcRn-/-,+huFcRn cells; and
    d) assaying IgG catabolism by the mammalian cells in the presence and absence of candidate inhibitor, with an increase in IgG catabolism in the presence of candidate inhibitor, as compared to IgG catabolism in the absence of candidate inhibitor, being an indication that the candidate inhibitor inhibits huFcRn.

30. A method to identify or characterize an inhibitor of IgG protection by huFcRn comprising:
    a) providing an FcRn -/-, +huFcRn transgenic mouse;
    b) administering tracer human IgG and tracer human IgA to the mouse;
    c) administering candidate inhibitor to the mouse; and
    d) determining the half-life of the tracer human IgG and tracer human IgA in the mouse which has received the candidate inhibitor as compared to the half-life of administered tracer human IgG and tracer human IgA in a FcRn -/-, +huFcRn transgenic mouse which has not received inhibitor, with a decrease in the half-life of the tracer human IgG, but not the tracer human IgA, in the mouse which has received candidate inhibitor, as compared to the half lives in the mouse which has not received candidate inhibitor, being an indication that the candidate inhibitor inhibits FcRn protection of IgG.

31. A method to inhibit FcRn mediated IgG protection in an individual comprising:
    a) providing a monoclonal antibody which specifically binds huFcRn through its antigen binding regions and inhibits binding of huFcRn to IgG; and
    b) administering the monoclonal antibody of step a) to the individual in sufficient amounts to inhibit binding of huFcRn of the individual to IgG of the individual.

32. The method of Claim 31 wherein the individual has an autoimmune disease.

33. The method of Claim 31 wherein the individual has the autoimmune disease systemic lupus erythematosus.

34. The method of Claim 31 wherein the autoimmune disease is selected from the group consisting of, but not limited to, insulin resistant diabetes, myasthenia gravis, polyarteritis, cutaneous vasculitis, pemphigus vulagaris, Goodpasture's syndrome, rheumatoid arthritis, Kawasaki's disease, and Sjogren's syndrome.

35. A method to inhibit FcRn mediated IgG protection in an individual, comprising:
    a) providing an engineered molecule comprising an Fc region of IgG to which the FcRn binds; and
    b) administering the engineered molecule of step a) to the individual in sufficient amounts to competitively inhibit binding of FcRn of the individual to IgG of the individual.

36. The method of Claim 35 wherein the individual has an autoimmune disease.

37. The method of Claim 35 wherein the autoimmune disease is lupus erythematosus.

38. The method of Claim 35 wherein the autoimmune disease is selected from the group consisting of, but not limited to, insulin resistant diabetes, myasthenia gravis, polyarteritis, cutaneous vasculitis, pemphigus vulgaris, goodpasture's syndrome, rheumatoid arthritis, kawasaki's disease, and sjogren's syndrome.

39. A method to inhibit FcRn mediated IgG protection in an individual, comprising:
    a) providing an organic molecule which binds to FcRn and inhibits binding of huFcRn to IgG; and
    b) administering the organic molecule of step a) to the individual in sufficient amounts to inhibit binding of FcRn of the individual to IgG of the individual.

40. A method to inhibit FcRn mediated IgG protection in an individual, comprising:
    a) providing an inhibitor of FcRn expression to the individual; and
    b) administering the inhibitor of step a) to the individual in sufficient amounts to inhibit expression of FcRn.

41. The method of Claim 40 wherein the inhibitor inhibits expression of FcRn at the transcription, translation, post-translational processing or protein transport to the membrane.

42. The method of Claim 40 wherein the inhibitor includes, but is not limited to, antisense oligonucleotides, reverse gene constructs, and specific targeting of regulator proteins.

43. A method to identify or characterize a therapeutic agent in the treatment of autoimmune diseases in humans, comprising:
    a) providing a mouse model of Claim 14;
    b) administering a candidate therapeutic agent to the transgenic mouse of step a); and
    c) monitoring autoimmune disease development in the transgenic mouse which receives the candidate therapeutic agent, with amelioration in autoimmune disease development, as compared to autoimmune disease development in a transgenic mouse of step a) which does not receive the candidate therapeutic agent, being an indication that the candidate therapeutic agent may be useful for treating autoimmune diseases in humans.

44. A method to identify or characterize a therapeutic agent in the treatment of autoimmune diseases in humans, comprising:
    a) providing a mouse model of Claim 18;
    b) administering a candidate therapeutic agent to the transgenic mouse of step a); and
    c) monitoring autoimmune disease development in the transgenic mouse which receives the candidate therapeutic agent, with amelioration in autoimmune disease development, as compared to autoimmune disease development in a transgenic mouse of step a) which does not receive the candidate therapeutic agent, being an indication that the

candidate therapeutic agent may be useful for treating autoimmune diseases in humans.

45. A method to identify or characterize a therapeutic agent in the treatment of autoimmune diseases in humans, comprising:
    a) providing a mouse model of Claim 22;
    b) administering a candidate therapeutic agent to the transgenic mouse of step a); and
    c) monitoring autoimmune disease development in the transgenic mouse which receives the candidate therapeutic agent, with amelioration in autoimmune disease development, as compared to autoimmune disease development in a transgenic mouse of step a) which does not receive the candidate therapeutic agent, being an indication that the candidate therapeutic agent may be useful for treating autoimmune diseases in humans.

46. A method to identify or characterize a therapeutic agent in the treatment of autoimmune diseases in humans, comprising:
    a) providing a mouse model of Claim 23;
    b) administering a candidate therapeutic agent to the transgenic mouse of step a); and
    c) monitoring autoimmune disease development in the transgenic mouse which receives the candidate therapeutic agent, with amelioration in autoimmune disease development, as compared to autoimmune disease development in a transgenic mouse of step a) which does not receive the candidate therapeutic agent, being an indication that the candidate therapeutic agent may be useful for treating autoimmune diseases in humans.

47. A method to identify or characterize a candidate agent for FcRn-mediated drug delivery, comprising:
    a) providing a formulation comprising a candidate agent for FcRn-mediated drug delivery attached to a trackable composition;
    b) administering the formulation to a muFcRn-/-, +huFcRn transgenic knockout mouse, and also to a muFcRn-/- transgenic knockout mouse; and
    c) assaying muFcRn-/-, +huFcRn transgenic knockout mouse and the muFcRn-/- transgenic knockout mouse for presence of the formulation in the bloodstream, with a substantially higher amount of the formulation in the bloodstream of the muFcRn-/-, +huFcRn transgenic knockout mouse as compared to the amount of the formulation in the bloodstream of the muFcRn-/- transgenic knockout mouse being an indication that the candidate agent facilitates FcRn-mediated drug delivery.

48. The method of Claim 47 wherein the candidate agent is derived from an immunoglobulin Fc region.

49. The method of Claim 47 wherein the candidate agent is derived from an FcRn binding partner, such as immunoglobulins or portions thereof.

50. The method of Claim 47 wherein the candidate agent is transported via the FcRn through the intestinal epithelium, mucosal epithelium, epithelium of the lung or transdermally.

51. The method of Claim 47 wherein the candidate agent is administered orally, as an aerosol, to pulmonary or nasal epithelial mucosal tissue, or transdermally.

52. A method to identify or characterize a candidate agent for FcRn-mediated drug delivery in the fetus or neonate, comprising:

a) providing a formulation comprising a candidate agent for FcRn-mediated drug delivery attached to a trackable composition;

b) administering the formulation to a either a neonate or pregnant muFcRn -/-, +huFcRn transgenic knockout mouse, and also to either a neonate or pregnant muFcRn -/- knockout mouse; and

c) assaying both the neonatal or fetal muFcRn -/-, +huFcRn and muFcRn -/- transgenic knockout mice for presence of the formulation in the bloodstream, with a substantially higher amount of the formulation in the bloodstream of the neonatal or fetal muFcRn -/-, +huFcRn transgenic knockout mouse as compared to the amount of the formulation in the bloodstream of the neonatal or fetal muFcRn -/- transgenic knockout mouse being an indication that the candidate agent facilitates FcRn-mediated drug delivery.

53. The method of Claim 52 wherein the candidate agent is derived from an immunoglobulin Fc region.

54. The method of Claim 52 wherein the candidate agent is derived from an FcRn binding partner, such as immunoglobulins or portions thereof.

55. The method of Claim 52 wherein the candidate agent is transported via FcRn through the intestinal epithelium, mucosal epithelium, epithelium of the lung or transdermally.

56. The method of Claim 52 wherein the candidate agent is administered orally, as an aerosol, to pulmonary or nasal epithelial mucosal tissue, or transdermally.

57. A method to identify or characterize a candidate agent for FcRn-mediated drug stabilization, comprising:
    a) providing a formulation comprising a candidate agent for FcRn-mediated drug stability attached to a trackable composition;
    b) administering the formulation to a muFcRn-/-, +huFcRn transgenic knockout mouse, and also to a muFcRn-/- transgenic knockout mouse; and
    c) assaying the half-life of the formulation in the bloodstream of the muFcRn-/-, +huFcRn transgenic knockout mouse and the bloodstream of the muFcRn-/- transgenic knockout mouse, with a substantially longer half-life in the bloodstream of the muFcRn-/-, +huFcRn transgenic knockout mouse being an indication that the candidate agent promotes FcRn-mediated drug stabilization.

58. The method of Claim 57 wherein the candidate agent is derived from an immunoglobulin Fc region.

59. The method of Claim 57 wherein the candidate agent is derived from an Fc region or fragment thereof, or other molecules which are structurally-similar or similar in sequence identity to the Fc-region of IgG.

60. The method of Claim 57 wherein the candidate agent is structurally-similar or similar in sequence identity to the Fc-region of IgG, such that the engineered molecule binds with greater affinity to the FcRn protein.

61. A method for determining the pharmacokinetics of an agent linked to an FcRn-mediated drug stability candidate, comprising:

a) providing a trackable formulation comprising an agent linked to a candidate agent for FcRn-mediated drug stability;

b) administering the formulation to a muFcRn-/-, +huFcRn transgenic knockout mouse,

c) determining the half-life of the formulation in the bloodstream of the muFcRn-/-, +huFcRn transgenic knockout mouse, as compared to the half-life of the agent, formulated without the candidate agent for FcRn-mediated drug stability; and

d) comparing the half-lives determined in step c) to one another to determine the difference in half-life conferred to the agent by the candidate agent for FcRn mediated drug stability.

62. The method of Claim 61 wherein the candidate agent is derived from an immunoglobulin Fc region.

63. The method of Claim 61 wherein the candidate agent is derived from an Fc region or fragment thereof, or other molecules which are structurally-similar or similar in sequence identity to the Fc-region of IgG.

64. The method of Claim 61 wherein the candidate agent is structurally-similar or similar in sequence identity to the Fc-region of IgG, such that the engineered molecule binds with greater affinity to the FcRn protein.

65. A method to identify or characterize a candidate agent for FcRn-mediated drug stabilization in a high-throughput system, comprising:

a) providing a formulation comprising a candidate agent for FcRn-mediated drug stabilization attached to a trackable composition;
b) administering the formulation to cells derived from muFcRn-/-, +huFcRn and muFcRn-/- or other mammalian cell lines which do not express FcRn; and
c) assaying the half-life of the formulation in cell media from cells in b), with a substantially longer half-life in the media from the muFcRn-/-, +huFcRn cells being an indication that the candidate agent promotes FcRn-mediated drug stabilization.

66. The method of Claim 65 wherein the candidate agent is derived from an immunoglobulin Fc region.

67. The method of Claim 65 wherein the candidate agent is derived from an Fc region or fragment thereof, or other molecules which are structurally-similar or similar in sequence identity to the Fc-region of IgG.

68. The method of Claim 65 wherein the candidate agent is structurally-similar or similar in sequence identity to the Fc-region of IgG, such that the engineered molecule binds with greater affinity to the FcRn protein.

69. A method to identify or characterize a candidate agent for FcRn-mediated drug stabilization in a high-throughput system, comprising:
a) providing a formulation comprising a candidate agent for FcRn-mediated drug stabilization attached to a trackable composition;
b) administering the formulation to mammalian cells expressing huFcRn mammalian cell lines and

mammalian cell lines which do not express FcRn; and

c) assaying the half-life of the formulation in cell media from cells in b), with a substantially longer half-life in the media from the mammalian cells expressing huFcRn being an indication that the candidate agent promotes FcRn-mediated drug stabilization.

70. The method of Claim 69 wherein the candidate agent is derived from an immunoglobulin Fc region.

71. The method of Claim 69 wherein the candidate agent is derived from an Fc region or fragment thereof, or other molecules which are structurally-similar or similar in sequence identity to the Fc-region of IgG.

72. The method of Claim 69 wherein the candidate agent is structurally-similar or similar in sequence identity to the Fc-region of IgG, such that the engineered molecule binds with greater affinity to the FcRn protein.

73. A method for determining the pharmacokinetics of an agent linked to an FcRn-mediated drug stability candidate, comprising:

a) providing a trackable formulation comprising an agent linked to a candidate agent for FcRn-mediated drug stability;

b) administering the formulation to cells derived from muFcRn-/-, +huFcRn and muFcRn-/- or other mammalian cell lines which do not express FcRn; and

c) assaying the half-life of the formulation in cell media from cells in b), with a substantially longer half-life in the media from the muFcRn-/-,

+huFcRn cells being an indication that the candidate agent promotes FcRn-mediated drug stabilization.

74. The method of Claim 73 wherein the candidate agent is derived from an immunoglobulin Fc region.

75. The method of Claim 73 wherein the candidate agent is derived from an Fc region or fragment thereof, or other molecules which are structurally-similar or similar in sequence identity to the Fc-region of IgG.

76. The method of Claim 73 wherein the candidate agent is structurally-similar or similar in sequence identity to the Fc-region of IgG, such that the engineered molecule binds with greater affinity to the FcRn protein.

77. A method for determining the pharmacokinetics of an agent linked to an FcRn-mediated drug stability candidate, comprising:

a) providing a trackable formulation comprising an agent linked to a candidate agent for FcRn-mediated drug stability;

b) administering the formulation to mammalian cells expressing huFcRn mammalian cell lines and mammalian cell lines which do not express FcRn; and

c) assaying the half-life of the formulation in cell media from cells in b), with a substantially longer half-life in the media from the mammalian cells expressing huFcRn being an indication that the candidate agent promotes FcRn-mediated drug stabilization.

78. The method of Claim 77 wherein the candidate agent is derived from an immunoglobulin Fc region.

79. The method of Claim 77 wherein the candidate agent is derived from an Fc region or fragment thereof, or other molecules which are structurally-similar or similar in sequence identity to the Fc-region of IgG.

80. The method of Claim 77 wherein the candidate agent is structurally-similar or similar in sequence identity to the Fc-region of IgG, such that the engineered molecule binds with greater affinity to the FcRn protein.